

PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

PCT

To:

see form PCT/ISA/220

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY (PCT Rule 43bis.1)

Date of mailing
(day/month/year) see form PCT/ISA/210 (second sheet)

Applicant's or agent's file reference
see form PCT/ISA/220

FOR FURTHER ACTION
See paragraph 2 below

International application No.
PCT/GB2004/002706

International filing date (day/month/year)
24.06.2004

Priority date (day/month/year)
24.06.2003

International Patent Classification (IPC) or both national classification and IPC
C07H5/10, C12N9/56, C12N9/44

Applicant
ISIS INNOVATION LIMITED

1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☐ Box No. II Priority
- ☐ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☒ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☒ Box No. VI Certain documents cited
- ☐ Box No. VII Certain defects in the international application
- ☐ Box No. VIII Certain observations on the international application

2. FURTHER ACTION

If a demand for international preliminary examination is made, this opinion will usually be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA"). However, this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notified the International Bureau under Rule 66.1bis(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of three months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

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WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITYInternational application No.
PCT/GB2004/002706

IAP20 Rec'd PCT/PTO 22 DEC 2005

Box No. 1 Basis of the opinion

1. With regard to the language, this opinion has been established on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.
☐ This opinion has been established on the basis of a translation from the original language into the following language , which is the language of a translation furnished for the purposes of international search (under Rules 12.3 and 23.1(b)).
2. With regard to any nucleotide and/or amino acid sequence disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:
 - a. type of material:
☐ a sequence listing
☐ table(s) related to the sequence listing
 - b. format of material:
☐ in written format
☐ in computer readable form
 - c. time of filing/furnishing:
☐ contained in the international application as filed.
☐ filed together with the international application in computer readable form.
☐ furnished subsequently to this Authority for the purposes of search.
3. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.
4. Additional comments:

**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY**

International application No.
PCT/GB2004/002706

Box No. VI Certain documents cited

1. Certain published documents (Rules 43*bis*.1 and 70.10)
and /or
2. Non-written disclosures (Rules 43*bis*.1 and 70.9)
see form 210

- 1) The present application relates to methods and reagents for disulfide bond formation, in particular for glycosylating proteins using thiosulfonates which are not alkylthiosulfonates or selenylsulfides.
- 2) Cited documents:
 - D1: CAPLUS AN: 1955:53561
 - D2: J.ORG.CHEM., vol. 36, no. 2, 1971, pages 309-313,
 - D3: ARZN.FORSCH./DRUG RES., vol. 40, no. 3, 1990, pages 282-286
 - D4: TET. LETT., vol. 31, no. 42, 1990, pages 6075-6076,
 - D5: WO 00/01712 A
 - D6: J.ORG.CHEM., 2000, vol. 65, no. 15, pages 4607-4617
 - D7: J.ORG.CHEM., vol. 51, no. 15, 1986, pages 2981-2988,
 - D8: ORG.BIOMOL.CHEM., vol. 1, no. 21, (2003-11-07), pages 3642-3644
 - D9: ANG.CHEMIE (INT.), vol. 43, no. 7, (2004-02-06), pages 828-833.

The priority of 24.6.03 seems valid for claims 1-17 and the priority of 12.12.03 seems valid for claims 18-29. Accordingly, D8 is only prior art with respect to claims 18-29, whereas D9 is not considered as prior art.

- 3) Novelty
- 3.1 Documents D1-D4 describe various thiosulfonates, including phenylthiosulfonates, for forming disulfide bonds with thiol-group comprising compounds, including aminoacid derivatives. In view of D1-D4 the subject-matter of claims 1-3,5,7,15 and 16 cannot be considered new.
These documents do not specifically describe the carbohydrate derivatives defined in claims 8-9,11-13 and 17 nor selenosulfide related compounds/reactions.

Document D6 describes a selenosulfide according to claims 8-10; this document does not, describe its application for preparing disulfide compounds nor its preparation as defined in present claim 14.

Document D7 describes the reaction of a selenosulfide with a thiol producing a disulfide, which is considered to anticipate the subject-matter of claims 1, 6 and 15.

- 3.2 Document D5 describes alkylthiosulfonates for forming disulfide bonds, in particular for glycosylating proteins, which is excluded from the present application.

Document D8 (only prior art for claims 18-29) describes the use of phenylthiosulfonates for preparing disulfide compounds without mention of selenosulfide compounds.

Document D9 describes selenosulfides in preparing disulfide compounds; this document is however not considered as prior art.

4) Inventive step

With respect to the new subject-matter document D5 may be considered as closest prior art. The problem to be solved may be seen in the provision of alternative agents for introducing disulfide linked groups, in particular carbohydrate-moieties. As solution the claimed matter would at present seem obvious to the person skilled in the art in view of D1-D4 (for thiosulfonates) and D7 (for selenosulfides) as these documents already describe various other thiosulfonates and selenosulfides as convenient reagents for the introduction of disulfide linked moieties.

With respect to claim 14 it is noted that document D6 may be considered as closest prior art. The alternative method for preparing this compound seems to reflect basic chemistry and would therefor prima facie not seem to involve an inventive step.

- 5) No unifying common distinguishing feature with respect to document D5, relating to related preparative methods, is evident between the subject-matter involving thiosulfonates on the one hand and selenosulfides on the other hand is evident. Furthermore, no common distinguishing feature with respect to D6 is evident amongst new selenosulfides and their application on the one hand and new methods for preparing (partly) known selenosulfides (claim 14) on the other hand.